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(54) Title: BREATH MALODOUR REDUCTION

(57) Abstract

The invention relates to a method for reducing breath malodour which comprises treating the oral cavity with a composition which contains at least one amino acid chosen from Leucine, Isoleucine, Glutamic acid and Asparagine (Group I) and/or from Tyrosine, Glycine, Phenylalanine, Valine, Histidine and Serine (Group II), and/or from Aspartic acid, Threonine, Alanine, Proline, Methionine, Tryptophan and Ornithine (Group III). Preferably the composition contains at least two amino acids from Group I and also at least one of each of Groups II and III. The oral cavity is preferably treated such that the fluid in it contains at least 0.1 g/l of the amino acids for at least 0.5 minutes. The invention also concerns suitable compositions for treating the oral cavity.

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Breath malodour reduction

The invention relates to methods for the reduction of breath malodour and compositions to be used therefore. In particular the inventions relates to the use of certain amino acids for reducing breath malodour.

Breath malodour, also called halitosis, is a common inconvenience. Although the condition may be exacerbated by certain disorders in the oral cavity (caries, gingivitis or periodontal disease), throat or lungs, or the alimentary tract, it should be stressed that breath malodour is a normal phenomenon in healthy individuals, especially after awakening (morning breath). In healthy individuals it is generally assumed that the major contribution to breath malodour comes from the oral cavity and that it is mainly caused by protein degradation by bacteria covering the hard and soft tissues in the mouth which leads to the formation of volatile sulphur compounds such as H_2S and CH_3SH, see e.g. J. Tonzetich, J. Periodontol. **48** (1977), 13-20 and I. Kleinberg, G. Westbay, Critical Reviews in Oral Biology and Medicine, **1** (1990), 247-259. The Gram-negative bacterial component of oral microflora has been held mainly responsible for oral malodour production, see: T.F. McNamara et al., Oral Surg. **34** (1972), 42, and M.C. Solis-Gaffar et al., J. Soc. Cosmet. Chem., **30** (1979), 241.

The oral flora contains both Gram-negative and Gram-positive bacteria. The Gram-positive bacteria are mainly **Streptococci**, which account for 30-60% of the bacterial population on surfaces of teeth, tongue, cheeks and in saliva, see P. Marsh and M. Martin, Oral Microbiology (third edition, 1992), p.68. These microorganisms are facultative anaerobes and may be found abundantly in dental plaque, together with anaerobic bacteria. However,

so far **Streptococci** have not been associated in the literature with breath malodour formation on a significant scale, see also S. Persson et al. Oral Microbiol Immunol. 1990: 5, 195-201.

Various methods are known for combatting malodours in general, and body and breath malodours in particular. The most common method consists of odour masking i.e. applying substances having an agreeable odour in such concentrations that the malodour is not noticed any more. In most cases this provides only temporary relief, especially for breath malodour since only limited amounts of masking odorants (mostly minty flavours) may be applied to the oral cavity.

Another way of combatting malodours has been described in WO-A 91/11988, which comprises offering an alternative substrate to the bacterial enzyme system which is responsible for decomposing cysteine and methionine into volatile sulphur compounds. This substrate is an amino acid derivative of the general formula $HOOC-CHNH_2-CH_2-X$, wherein X is OR or SR with R being chosen such that after decomposition of this new substrate a compound with little odour or even a pleasant odour remains. Furthermore, the use of green tea flavonoids in chewing gum to combat breath malodour is decribed by Y. Sato et al. Shokuhin Kogyo 30(24) (1987), 43-51.

EP-A-0 204 017 describes a deodorant product for various applications. It is said to be suitable for foods, cosmetics, rooms, household products and oral hygiene products. It comprises a residue obtained by removing water and alcohol from a beverage obtained by fermentation. Examples of such beverages are wine, beer, sake etc and are collectively referred to in the patent application as "brewed wine". Also an extract of the

evaporation residue or the residue or lees obtained after the fermentation process may be used. Hereinafter the products described in EP-A-0 204 017 and referred to above are collectively referred to as "brewed wine derivatives". In addition to the brewed wine derivatives, the malodour counteracting products described in EP-A-0 204 017 may also contain certain amino acids, amino acid salts or dipeptides. The brewed wine derivatives will invariably have a strong flavour, akin to but much stronger than the flavour of the beverage from which they are derived. Therefore, the products according to EP-A-0 204 017 are hardly, if at all, suitable for use in the oral cavity.

It has been found that the Streptococcal flora of the oral cavity abundantly produce H_2S under anaerobic conditions and thus give a large contribution to breath malodour. Thus, there is a need for new methods and compositions suitable for reducing breath malodour, especially breath malodour produced by **Streptococci** in the oral cavity.

According to the present invention, breath malodour produced by **Streptococci**, and in particular **Streptococcus sanguis**, **Streptococcus salivaris** and **Streptococcus mitior**, may be reduced by treating the oral cavity with certain amino acids or amino acid mixtures.

Thus, the invention concerns a method for reducing breath malodor comprising treating the oral cavity with a composition comprising at least one amino acid chosen from the group consisting of: Leucine, Isoleucine, Glutamic acid and Asparagine, which group is hereinafter referred to as "group I", and/or at least one amino acid chosen from the group consisting of: Tyrosine, Glycine, Phenylalanine, Valine, Histidine and Serine, which group is hereinafter referred to as "group II", and/or at least one amino acid chosen from the group consisting of

Aspartic acid, Threonine,Alanine, Proline, Methionine, Tryptophan and Ornithine, which group is herinafter referred to as "group III".

Accordingly, the invention also concerns the use of at least one amino acid chosen from group I and/or group II and/or group III for preparing a composition for reducing breath malodour.

Furthermore, the invention concerns compositions for reducing breath malodour comprising at least one amino acid chosen from group I and/or group II and/or group III.

The amino acids of group I, group II and group III are able to largely suppress the formation of H_2S by **Streptococci** grown under anaerobic conditions. The group I amino acids were found to be more active than the group II amino acids, which were in turn more active than the group III amino acids. Leucine was found to be most effective of all. Furthermore, a combination of at least two amino acids of group I is preferred. It is further preferred to have one or more group II amino acid present as well and it is even more preferred to also have one or more Group III amino acids present.

The effect not only lasts while the bacteria remain in contact with the amino acids but lingers on after the amino acids have been removed. Thus, for effective reduction of breath malodour for a considerable period of time it is sufficient if the oral cavity is treated for a limited period of time with a composition comprising the amino acids according to the invention. In general, useful reduction of breath malodour is obtained if the **Streptococci** in the oral cavity remain in contact with a total concentration of group I and/or group II and/or group III amino acids of at least 0.1 g/l, preferably at

least 0.4 g/l for a period of at least 0.5 minutes. Preferably a concentration of group I amino acids of at least 0.1 g/l is maintained as part of the total concentration of amino acids from groups I-III. More pronounced reduction is obtained if the total amino acid concentration is at least 2g/l or even more preferred at least 4 g/l. Also, or alternatively, the contact period may be prolonged, preferably to at least 2 minutes, more preferably to at least 5 minutes.

To this end oral cavity fluid should contain the desired concentration of the amino acids for the desired period of time. Oral cavity fluid may be the saliva in the mouth, in which case the saliva should contain this concentration for the desired period of time. This may be done by any suitable means, e.g. through tooth paste, chewing gum, candy or the like containing the amino acids in a suitable amount. Alternatively it may be done by putting a fluid containing this amino acid concentration in the oral cavity in the form of a drink, mouth wash or the like, which is kept in the mouth for a sufficient period of time and thus acts as oral cavity fluid.

The amino acids or mixtures of amino acids used in the method according to the invention and comprised in the compositions according to the invention may be pure, i.e. devoid of any other amino acid, or they may be in admixture with other amino acids. Such other amino acids do not interfere with the purposes of the invention; even complex mixtures of amino acids such as obtained by hydrolysis of proteins may be used, provided they contain the required amino acids in the required quantities. The desired amino acids may also be present in the form of simple peptides e.g. dipeptides. However, brewed wine derivatives as described in EP-A-0 204 017 do not serve any useful purpose in the invention and in view of their

organoleptic properties should preferably be absent from the compositions used in the invention.

As will be clear from the above, the compositions used in the method according to the invention should contain the desired amino acids of group I and/or group II and/or group III, preferably group I, more preferably groups I and II, still more preferably groups I, II and III, as outlined above, in quantities sufficient to provide oral cavity fluid with the required concentration of amino acids for the required period of time. To this end the compositions preferably contain at least 0.01% w/w of these amino acids. For organoleptic reasons the compositions are preferred to contain not more than 10% w/w of amino acids. More preferably the composition should contain at least 0.04% w/w whereas generally a maximum of 2% w/w is sufficient. Furthermore, to make such compositions more attractive from a consumer point of view, as well as further improve their perceived action, they will generally contain a flavour which has a refreshing action on mouth and breath. Such flavours will in most cases be of the minty type, e.g. having peppermint, spearmint and/or menthol-like flavour notes. Occasionally fruit flavours may be used as well. Such flavours are hereinafter collectively referred to as "dental flavour"

The compositions according to the invention may be given the form of products well known in the art for medicinal or hygienic treatment of the oral cavity or the teeth such as tooth pastes, mouth washes and the like. Such products may be produced with ingredients and according to processes and procedures known in the art such as described e.g. in "Harry's Cosmeticology", Seventh Edition 1982, edited by J.B. Wikinson et al, pages 609-617.

Alternatively, compositions according to the invention may be in the form of chewing gum or candies or the like or a refreshing drink. Ingredients, processes and procedures for producing these products are again well known in the art and e.g. for chewing gum described in "Gum Bases and Gum Products Technology", published by Cafosa Gum S/A, Barcelona, Spain and in "The Great American Chewing Gum Book", Robert Hendrickson, 1974.

The invention is further illustrated by the Examples given below:

Example 1

The ability of **Streptococci** to produce H_2S under aerobic and anaerobic conditions was determined in vitro using the conditions given below:

The experiments were carried out in 10 ml or 20 ml Chrompack vials half-filled with chemically defined medium according to S. Socransky et al.,J. Clin. Microbiol. **22**(2) (1985), 303-305, but modified as outlined below. The medium in the vials was inoculated with **Streptococci** from an internal and external library of oral microflora. The vials were sealed with teflon-coated silicone rubber septa permitting overgassing/degassing of samples to provide an anaerobic (N_2) or aerobic (O_2) environment. The headspace was sampled after puncturing of the self-sealing septum with a gas-tight syringe. Inoculated vials were incubated at 30°C and analysed at specific time intervals.

H_2S in the headspace was determined by GC analysis on a Perkin- Elmer 8000 series 2 GC fitted with a 30m x 0.53mm SPB-1 fused silica (3.0 μm film thickness) capillary column. The column output was split equally between a

flame ionisation (FID) and a flame photometric (FPD) detector. The output of the FPD was linearised and calibrated to read ng/ml levels of H_2S directly from 100µl headspace gas samples, The injector and detector were held at 140°C and 250°C respectively while the oven temperature was maintained at 35°C throughout each analysis run.

Modified Socransky medium used for culturing the **Streptococci:**

Basal medium (g/l): KNO_3 (0.1); KH_2PO_4 (1.0); K_2HPO_4 (1.5); NaCl (0.1); $(NH_4)_2PO_4$ (2.0);

Vitamins (mg/l): nicotinic acid (1.0); nicotinamide (1.0); NADH (1.0); folic acid (1.0); calcium pantothenate (1.0); reboflavin (1.0); thiamine-HCL (1.0); spermine tetrahydrochloride (1.0); spermine trihydrochloride (1.0); putrescine dihydrochloride (1.0); pimelic acid (0.1); D,L-mevalonc acid lactone (0.1); D-mevalonic acid lactone (0.1); biotin (0.1); p-aminobenzoic acid (0.1); lipoic acid (0.1); B-alanine (10.0); myo-inositol (10.0); choline chloride (50.0);

Pyridoxal species (mg/l): pyridoxal (1.0); pyridoxal-HCL (1.0); pyridoxamine dihydrochloride (1.0).

Purines/pyrimidines (mg/l): adenine (10.0); guanine (10.0); cytosine (10.0); thymine (10.0); xanthine (10.0); hypoxanthine (10.0); uracil (10.0);

Salts (mg/l): KI 94.0); $CuSO_4$(1.0); H_3BO_3 (0.4); $FeSO_4$ (5.0); $MnSO_4$ (50.0); Na_2MoO_4 (5.0);

Other additions: hemin (5.0 mg/l); glucose (4.0 g/l); $CaCl_2$ (10 mg/l); $MgSO_4$ (0.7 g/l); $NaHCO_3$ (1.0 g/l);

Amino acids (mg/l): glutamate (40); glutamine (20); proline (20); arginine (20); ornithine (5); hydroxyproline (5); aspartate (20); methionine (200); threonine (20); isoleucine (20); asparagine (20); lysine (20); tryptophan (20); phenylalanine (20); tyrosine (5); serine (20); glycine (20); cysteine (200); cystine (6.25); alanine

(20); valine (20); leucine (20); histidine (20). **(Total non-sulphur amino acid concentration 0.4 g/l).**

The amount of H_2S in the headspace produced by various oral **Streptococci** species under aerobic and anaerobic conditions is presented in Table I below:

Table I

Streptococcus species	(ng/ml H_2S) anaerobic	(ng/ml H_2S) aerobic
S. salivarius NCTC 8618	159	0.45
S. gordinii NCTC 10231	83	0.0
S. mutans NCTC 10449	1540	0.8
S. anginosus NCTC 10715	61	0.2
S. mutans	49	0.1
S. sanguis	244	0.1
S. salivarius	43	0.1
S. mitior	177	0.1
cell-free control	0.2	-

Example 2

The effect of various amino acid mixtures on H_2S production by **Streptococcus sanguis** was tested using the conditions specified in Example 1 with the proviso that the culture medium contained 200 mg/l cysteine but no other amino acids apart from the mixture added for test purposes. The test mixtures I and II consisted of equal amounts of all amino acids of group I and of group II respectively. Each mixture as well as a combination of both mixtures with a mixture of all group III amino acids were tested in concentrations of 0.4, 2.0 and 4.0 g/l with a control containing only cysteine (amino acids: 0 g/l).

The amount of H_2S in the headspace (in ng/ml) for each test mixture is given after incubation for 2.5 and 20 hours.

The results are presented in Table II below.

Table II

H_2S generation by S. sanguis in ng/ml

Group	time in hours	amino acid concentration (g/l)			
		0	0.4	2.0	4.0
I	2.5	411	64	30	18
	20	915	428	131	59
II	2.5	411	142	45	39
	20	915	268	112	45
I+II+III	2.5	411	39	9	6
	20	915	86	31	23

Example 3

The effect of individual amino acids of group I on H_2S production by **Streptococcus sanguis** was tested using the conditions specified in Example 1 with the proviso that the culture medium contained 200 mg/l cysteine but no other amino acids apart from the one added for test purposes. Each amino acid was tested in concentrations of 2.0 and 4.0 g/l with a control containing only cysteine (amino acid: 0 g/l). The amount of H_2S in the headspace (in ng/ml) for each test mixture is given after incubation for 3 and 18 hours is given in Table III below.

Table III

H_2S generation by S. sanguis in ng/ml

Amino acid	Time (hours)	Concentration in g/l		
		0	2	4
Leucine	3	756	179	99
	18	1268	100	65
Isoleucine	3	756	162	120
	18	1268	167	122
Asparagine	3	756	228	174
	18	1268	221	116
Glutamic acid	3	756	190	221
	18	1268	360	370

Example 4

The effect of various protein hydrolysates on H_2S production by Streptococcus sanguis was tested using the conditions specified in Example 1 with the proviso that the culture medium contained 200 mg/l cysteine but no other amino acids apart from the protein hydrolysates added for test purposes. Each protein hydrolysate was tested in concentrations of 5.0 and 20.0 g/l. The amount of H_2S in the headspace (in ng/ml) for each test mixture after incubation for 4 and 18 hours is given in Table IV below. The results for 5.0 g/l of the amino acid mixture of group I are presented as well.

Table IV

H_2S generation by S. sanguis in ng/ml

Protein hydrol. or amino acid mixture	Time (hours)	Conc. of protein hydrolysate or amino acids in g/l		
		0	5	20
Primatone SG	4 18	554 713	45 62	23 30
Hycase SF	4 18	554 713	15 6	8 12
N-Z Amine YT	4 18	554 713	16 12	16 20
Group I	4 18	554 713	25 21	

Example 5

The effect of a short treatment of S. sanguis with amino acids on the production of H_2S was tested by suspending the cells in the modified Socransky medium according to Example 1 with the proviso that it contained 200mg/l of cysteine but no other amino acids/protein hydrolysates than the ones added for test purposes in the amounts indicated. After 5 minutes the cells were separated from the medium and resuspended in modified Socransky medium containing only the cysteine and no other amino acids at all, and H_2S production monitored after 2, 5 and 24 hours. The results in Table V show that even after a short contact time of 5 minutes an appreciable reduction of malodour production is obtained as compared to test samples which had not been contacted with amino acids (apart from cysteine) before resuspension.

Table V

Contact Medium	H_2S levels in ng/ml after culture time in hours		
	2	5	24
Hyprol 8360			122
Hyprol 5111			170.6
Hycase SF (5g/l)	142	250	272
Group I (4g/l)	33	83	62
no amino acids (control)	230	405	446

Example 6

The effect of a combination of amino acids of Groups I, II and III together on H_2S production of various **Streptococci** from an internal and an external library of oral microflora was tested using the conditions of Example 2 with the amino acid mixture specified on page 8 such that a total non-sulphur amino acid concentration of 0.4 and 2.0 g/l respectively was obtained and a control containing no amino acid (0 g/l) apart from cysteine. The incubation was continued for 20 hours. The results are presented in Table VI below.

Table VI

H_2S generation by various Streptococci in ng/l

Micro-organisms	Amino Acid Concentration (g/l)		
	0	0.4	2.0
S. salivarius G5	887.9	184.1	2.5
S. salivarius NCTC 8618	173.1	6.91	2.0
S. Mutans G2	225.1	0.93	1.0
S. gordonii NCTC 10231	40.1	0	0
S. mutans G94	388.1	32.1	0,6
S. sanguis G4	689.5	226.9	27.6
S. mittior G6	410.5	30.9	8.9
S. mutans NCTC 10449	586.3	2.6	2.3
S. ovalis G93	411.8	76.2	25.5
S. anginosus NCTC 10715	38.9	6.7	1.3
Cell free control	0.7	0.1	0.3

CLAIMS

1. Method for reducing breath malodor comprising treating the oral cavity with a composition comprising at least one amino acid chosen from group I consisting of: Leucine, Isoleucine, Glutamic acid and Asparagine and/or at least one amino acid chosen from group II consisting of: Tyrosine, Glycine, Phenylalanine, Valine, Histidine and Serine, and/or at least one amino acid chosen from group III consisting of Aspartic acid, Threonine,Alanine, Proline, Methionine, Tryptophan and Ornithine .

2. Method according to claim 1 characterized in that the composition contains no brewed wine derivatives.

3. Method according to claim 1 or 2 characterized in that the amino acid is chosen from group I.

4. Method according to claim 3 characterized in that the amino acid is Leucine.

5. Method according to any one of claims 1-4 characterized in that the composition comprises at least two amino acids from group I.

6. Method according to any one of claims 3-5 characterized in that the composition also comprises one or more amino acids chosen from group II

7. Method according to any one of claims 3-6 characterized in that the composition also comprises one or more amino acids chosen from group III

8. Method according to any one of claims 1-7 characterized in that the total concentration of

group I, II and III amino acids in the oral cavity fluid is maintained at at least 0.1 g/l for at least 0.5 minutes.

9. Method according to claim 8 characterized in that the total concentration of amino acids is at least 0.4 g/l and the concentration of group I amino acids is at least 0.1 g/l.

10. A composition for reducing breath malodor comprising a dental flavour and at least one amino acid chosen from group I consisting of: Leucine, Isoleucine, Glutamic acid and Asparagine and/or at least one amino acid chosen from group II consisting of: Tyrosine, Glycine, Phenylalanine, Valine, Histidine and Serine, and/or at least one amino acid chosen from group III consisting of Aspartic acid, Threonine,Alanine, Proline, Methionine, Tryptophan and Ornithine .

11. A composition according to claim 10 characterized in that it contains no brewed wine derivatives.

12. A composition according to claim 10 or 11 characterized in that the amino acid is chosen from group I.

13. A composition according to claim 12 characterized in that the amino acid is Leucine.

14. A composition according to any one of claims 10-13 characterized in that it comprises at least two amino acids from group I.

15. A composition according to any one of claims 12-14 characterized in that it also comprises one or more amino acids chosen from group II

16. A composition according to any one of claims 12-15 characterized in that it also comprises one or more amino acids chosen from group III

17. A composition according to any one of claims 10-16 characterized in that it contains a total of at least 0.01% by weight of groups I and/or II and/or III amino acids.

18. A composition according to any one of claims 10-17 characterized in that the amino acids are comprised in a protein hydrolysate.

19. A composition according to any one of claims 10-18 which is a mouth wash composition.

20. A composition according to any one of claims 10-18 which is a tooth paste.

21. A composition according to any one of claims 10-18 which is a candy or chewing gum.

INTERNATIONAL SEARCH REPORT

Internation: pplication No
PCT/EP 95/03307

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/22 A23G3/30 A23G3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 238 918 (PROBIOS BIOTECHNOLOGIE GMBH) 30 September 1987 see page 4-5; claims 1,3,5,6,9; examples 2,3; table 1 ---	1-17, 19-21
X	PATENT ABSTRACTS OF JAPAN vol. 005 no. 016 (C-041) ,30 January 1981 & JP,A,55 143916 (SEIKENKAI) 10 November 1980,	1-3,5-7, 10-12, 14-17
A	see abstract & FR,A,2 352 057 (SEIKEN KAI FOUNDATION) see page 1-2; claims 1,2,4; tables 17,18 --- -/--	19-21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Internatior .pplication No
PCT/EP 95/03307

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 8348 Derwent Publications Ltd., London, GB; AN 83-829931 & JP,A,58 180 429 (MEIJI MILK PRODS KK) , 21 October 1983	10-18
A	see abstract	21

X	NL,A,6 812 850 (KYOWA HAKKO KOGYO KK) 11 March 1969 see page 1-2 & GB,A,1 245 468 (KYOWA HAKKO KOGYO KK) see page 2, left column; claims 1,6	1-7,9-17

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In.. .nation on patent family members

Internatio Application No
PCT/EP 95/03307

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-238918	30-09-87	DE-A- 3608423	17-09-87
		WO-A- 8705625	24-09-87
		JP-A- 62272970	27-11-87
NL-A-6812850	11-03-69	BE-A- 720378	17-02-69
		CH-A- 502070	31-01-71
		FR-A- 1578691	14-08-69
		GB-A- 1245468	08-09-71